

REMARKS/ARGUMENTS

This is a response to the Office Action dated 07 September 2005. Applicants are submitting a request for continued examination with this amendment and arguments.

Claims 96-97 and 99-107 are currently pending in the present application. Claims 1-95 and 98 have been cancelled. Claims 96 and 97 are independent claims. Claims 99-107 are multiple dependent claims dependent upon Claims 96 and 97. Claims 96-97 and 99-107 are rejected under 35 USC §103(a). In view of the following remarks and amendments, Applicants respectfully submit that all pending claims are now in condition for allowance.

1. 35 U.S.C. §103(a)

Claims 96-97 and 99-107 are rejected under 35 U.S.C. § 103(a) as being unpatentable over June et al. (WO 95/33823) in view of Chang et al. (U.S. Patent No. 6,129,916) (of record), Levine et al. (International Immunology 7: 891-904, 1995), Kwon et al. (U.S. Patent No. 6,569,997) (of record) and Allaway et al. (US 2004/0086528 A1) (of record).

Response

June et al. (WO95/33823) in view of Chang et al. (U.S. Pat. 6,129,916), Levine et al. (international Immunology 7:891-904, 1995), Kwon et al. (U.S. Pat. 5,569,997) and Alloway et al. (U.S. 2004/0086528 A1) fail to establish a prima facie case of obviousness under 35 USC 103(a) because the references as a whole do not teach each and every element of Claims 96-97 and 99-107.

Independent Claim 96 is drawn to an *ex vivo* method for down-regulating CCR5 expression in a T cell comprising contacting the T cell with a single bead comprising both an anti-CD28 antibody or antigen binding fragments and an anti-CD3 antibody or antigen binding

fragments immobilized on said bead; and measuring the level of CCR5 RNA or protein expression in said contacted T cell.

Independent Claim 97 is drawn to a method for down-regulating CCR5 RNA protein expression in a T cell, comprising contacting the T cell *in vivo* with a single bead comprising both an anti-CD28 antibody or antigen binding fragments and an anti-CD3 antibody or antigen binding fragments immobilized on the same bead; and measuring the level of CCR5 RNA protein expression in said contacted T cell. Claim 99-107 are multiple dependent claims of Claims 96 and 97.

The Office Action alleges that the combination of the primary reference, June et al. in view of Chang, Levine, Kwon and Allaway teach the beneficial effects of contacting T cells with anti-CD3 and anti-CD28 antibodies on a bead to increase HIV resistance and that the beneficial effect was a result of down regulation of CCR5. Thus one of skill in the art would have been motivated to combine the teachings of the references in order to induce an HIV resistant state and to monitor the expression of CCR5 expression as a result of the effect of combining anti-CD3 and anti-CD28 antibodies on T cell populations on HIV expression. It is also alleged that one of ordinary skill in the art at the time the invention was made would have been motivated to monitor the expression of CCR5 expression to monitor the effect of combining anti-CD3 and anti-CD28 antibodies on T cell populations on HIV expression. In addition, the Examiner found the prior art provides for the co-immobilization of anti-CD3 and anti-CD28 on the same bead as a means of stimulating T cells.

Applicants contend that June et al. teaches the proliferation of T cells by contacting the T cells with anti-CD3 and anti-CD28 antibodies immobilized on a microbead. Chang et al. and Levine et al. teach beads comprising multiple antibody specificities, including anti-CD3

antibodies and anti-CD28 antibodies. However, June et al. in view of Levine and Chang fail to address the effect of contacting T cells with bead immobilized anti-CD3 and anti-CD28 antibodies on CCR5 expression. The Examiner pointed to Kwon (particularly first paragraph, Col. 28) and found Kwon et al. teach that the ligation of T cells with anti-CD3 antibodies and anti-CD28 antibodies induce an HIV virus resistant state, which appears to be specific for macrophage-tropic HIV and appears to be the result of down-regulation of CCR5, the fusion cofactor. The examiner also found Allaway et al. teach various methods to measure CCR5, including in assays measuring the effects of inhibiting fusion of HIV-1 to CD4⁺ T cells and infection of the cells.


Applicants contend the combined references only provided an impetus to further explore how to obtain efficient induction of HIV resistance since besides Kwon fails to provide data supporting the suggestion linking down-regulation of CCR5 expression as a result of contacting T cells with anti-CD3 and anti-CD28 antibodies immobilized on beads. Furthermore, applicant contends that the state of art at the time this application is filed is not clear as to the effects using anti-CD3 and anti-CD28 antibodies on HIV infection. Figure 2 B and C of Roederer, M., Feb. 1997 (currently submitted) show that stimulation using immobilized anti-CD3/28 increases HIV replication from memory CD4 cells. Spina, C. A. Feb. 1997 (currently submitted) showed soluble Anti-CD3/CD28 antibodies increased HIV replication from cultures of human CD4 memory cells. Creson, 1999 (previously submitted), teaches using immobilized anti-CD3/CD28 antibodies on plastic increases HIV production from macrophage (CCR5) tropic HIV.

These references provided evidence showing that it would not have been obvious to one of ordinary skills in the art at the time this application was filed that anti-CD3 and anti-CD 28 antibodies must be immobilized on cell-sized bead to induce HIV resistance or such HIV

resistance is attributed to the down-regulation of CCR5 expression. One can only appreciate the very different effects of using immobilized anti-CD 3 and anti-CD28 antibodies on HIV infection and linking it to down-regulation of CCR5 after significant experimentation and study.

In view of the amendment to the claims and the above stated arguments, Applicants contend the case is now in condition for allowance. An early and favorable reply is requested.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Ning Yang', with a stylized, flowing script.

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